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# Is ABP1 an Auxin Receptor Yet?

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**ABSTRACT AUXIN BINDING PROTEIN 1 (ABP1) has long been proposed as an auxin receptor to regulate cell expansion. The embryo lethality of ABP1-null mutants demonstrates its fundamental role in plant development, but also hinders investigation of its involvement in post-embryonic processes and its mode of action. By taking advantage of weak alleles and inducible systems, several recent studies have revealed a role for ABP1 in organ development, cell polarization, and shape formation. In addition to its role in the regulation of auxin-induced gene expression, ABP1 has now been shown to modulate non-transcriptional auxin responses. ABP1 is required for activating two antagonizing ROP GTPase signaling pathways involved in cytoskeletal reorganization and cell shape formation, and participates in the regulation of clathrin-mediated endocytosis to subsequently affect PIN protein distribution. These exciting discoveries provide indisputable evidence for the auxin-induced signaling pathways that are downstream of ABP1 function, and suggest intriguing mechanisms for ABP1-mediated polar cell expansion and spatial coordination in response to auxin.**

**Key words: Hormonal regulation; hormone biology; receptors; signal transduction; cell signaling.**

## INTRODUCTION

In plants, the phytohormone auxin is essential to coordinate many growth and developmental processes at different levels. The asymmetric distribution of auxin regulates plant embryogenesis, morphogenesis, organogenesis, and reproduction (Leyser, 2006; Benjamins and Scheres, 2008). At the cellular level, auxin is responsible for cell division, expansion, and differentiation (Mockaitis and Estelle, 2008; Chapman and Estelle, 2009).

Given auxin's function in many diverse processes, the mechanisms of its perception and signaling transduction might be diverse as well. In the past decade, one milestone of auxin signaling research is the discovery of TIR1/AFB-based nuclear signaling (Dharmasiri et al., 2005a; Kepinski and Leyser, 2005). After entering the nucleus, auxin acts as a molecular glue to stabilize the interaction between the TIR1/AFB F-Box proteins and the AUX/IAA transcriptional repressor. Thereby, AUX/IAA is targeted for ubiquitination and subsequent degradation by the 26S proteasome. Degradation of AUX/IAA repressor results in the de-repression of many auxin-regulated promoters (Napier, 2005; Badescu and Napier, 2006; Mockaitis and Estelle, 2008). Although the $SCF^{TIR1/AFB}$ signaling pathway is responsible for the regulation of a great number of auxin responses, some rapid cellular auxin effects seem unlikely to be transcriptionally regulated (Barbier-Brygoo et al., 1989; Steffens et al., 2001; Yamagami et al., 2004; Badescu and Napier, 2006). Therefore, alternative auxin signaling pathways that account for the rapid auxin responses exist in plants as well.

Auxin binding protein 1 (ABP1) is a 22-kDa glycoprotein that is present in all green plants (Diekmann et al., 1995; Tromas et al., 2010). First detected in maize coleoptiles nearly 40 years ago (Hertel et al., 1972), ABP1 soon became a candidate auxin receptor (Lobler and Klambt, 1985; Jones and Herman, 1993; Brown and Jones, 1994; Jones et al., 1998; Timpte, 2001; Napier et al., 2002; Kramer, 2009; Tromas et al., 2010). ABP1 was shown to be essential for a wide variety of auxin-regulated processes, including cell division and expansion, auxin-regulated gene expression, and early auxin response at the plasma membrane (PM) (see references in Tromas et al., 2010). Despite confirmation of its auxin-binding activity by a series of biochemical experiments, the underlying signaling mechanism remained enigmatic for over 30 years (Venis et al., 1992; Thiel et al., 1993; Leblanc et al., 1999; Bauly et al., 2000). The C-terminus of ABP1 contains a KDEL sequence, which suggests the protein has an endoplasmic reticulum (ER) localization. However, in the rather neutral environment of ER, ABP1 has a very low auxin-binding affinity (Tian et al., 1995). A small portion of ABP1 is localized to the PM, which was proposed to be the major location of auxin perception by ABP1 (Jones and

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Herman, 1993; Tian et al., 1995; Henderson et al., 1997). If it acts as an auxin receptor, the low amount of PM-located ABP1 would have the potential to sense subtle changes in extracellular auxin levels, and then induce the downstream signaling cascades. As ABP1 lacks a transmembrane domain, its association with PM probably requires other membrane-bound 'docking protein' (Tromas et al., 2010). Up until now, the only candidate of this 'docking protein' is a glycosylphosphatidylinositol (GPI)-anchored protein named CBP1 (C-terminal peptide-binding protein 1), which was identified from maize seedling (Shimomura, 2006). CBP1's interaction and functional relationship with ABP1 have not been demonstrated. One possible function of CBP1 is to mask the ER retention signal localized at the C-terminus of ABP1 and thus to facilitate the secretion of ABP1. Primarily due to lack of knowledge about ABP1's mode of action, ABP1's role as an auxin receptor has been subject to debate for decades (Tromas et al., 2010).

Until recently, the embryo lethality of the null *abp1* mutant had been a major obstacle for characterizing ABP1-mediated auxin response in later developmental stages and for investigating the mechanisms underlying ABP1's action (Chen et al., 2001). The establishment of a system that allows conditional repression of ABP1 expression and the isolation of weak *abp1* alleles provided a unique opportunity to investigate the post-embryonic function of ABP1 and to identify the components that are downstream of ABP1-mediated auxin perception (Tromas et al., 2009; Robert et al., 2010; Xu et al., 2010). These recent studies will be the focus of this review, while the reader is referred to an excellent recent review for a more complete discussion of ABP1 (Tromas et al., 2010).

## ABP1 ALSO REGULATES CELL DIVISION AND AUXIN-INDUCED GENE EXPRESSION

Previous studies suggest that ABP1 regulates cell expansion (Jones et al., 1998; Steffens et al., 2001). Using an ethanol-inducible system to knock down ABP1 expression or to inhibit ABP1 function in *Arabidopsis thaliana* plants, Perrot-Rechenmann's group reported that ABP1 functions in multiple aspects of root and leaf growth or development, including cell division and elongation (David et al., 2007; Braun et al., 2008; Tromas et al., 2009)

The size of root meristem decreases substantially in ABP1-inactivated plants due to the contribution of both the arrested cell division and the early transition from stem cells to differentiated cells that are undergoing elongation (Tromas et al., 2009). The authors also showed that, although ABP1 does not seem to affect cell elongation in roots, its activity is essential for defining the region for the expression of *PLETHORA* (*PLT*) family genes, which encode AP2-domain transcription factors and regulate the transition from the meristem to the elongation zone. Overexpression of *PLT2* in ABP1-inactivated plants at an early stage inhibits cell elongation from the basal meristem; therefore, the plants restore the normal size of root meristem, indicating that PLTs act downstream of ABP1 to control the transition from meristem to elongation zone. However, overexpression of *PLT2* cannot restore the ability for cell division in already differentiated cells, suggesting that ABP1 controls cell division in a *PLT*-independent manner. Either overexpression of *CYCD3.1* or repression of *RBR* expression rescues the ABP1-mediated cell cycle arrest, suggesting that ABP1 controls the size of root apical meristem by mediating an auxin-dependent G1/S transition through the CYCD/RBR pathway (Wildwater et al., 2005; Tromas et al., 2009).

Interestingly, these studies further suggest that ABP1 also regulates the expression of AUX/IAA genes, which are known to be among early auxin-induced genes that are regulated by the TIR1/AFB pathways (Braun et al., 2008; Tromas et al., 2009). This raises an intriguing question regarding the functional relationship between ABP1 and TIR1/AFB. A portion of *tir1 afb1 afb2 afb3* siblings develop roots and leaves and are able to undergo normal reproductive development (Dharmasiri et al., 2005b), suggesting that additional auxin receptor(s) are still functional in this quadruple mutant. It is possible that the newly identified TIR1/AFB members, AFB4 and AFB5, functionally compensate their homologs (Greenham et al., 2011). It is equally tempting to propose that ABP1-mediated transcriptional responses could compensate for those regulated by TIR1/AFB-based signaling. It will be important to determine whether ABP1 acts on the PM or in the ER to regulate auxin-induced gene expression. In either case, auxin signal would need to be transmitted from one of these membrane systems to the nucleus for the regulation of gene expression, where TIR1/AFBs are thought to act. One candidate involved in the membrane-to-nucleus signaling is ROP/Rac GTPases, which have been reported to be activated by auxin and promote auxin-induced gene expression (Tao et al., 2002). Interestingly, ROPs have also been shown to regulate ABP1-dependent non-transcriptional auxin-responses, as discussed below.

## ABP1-MEDIATED AUXIN SIGNALING CONTROLS CELL MORPHOGENESIS

Xu and colleagues (2010) showed that ABP1-dependent auxin perception is required for the rapid activation of the antagonizing ROP2 and ROP6 pathways at the PM, and thereby regulates planar morphogenesis of pavement cells. The authors showed that exogenous auxin promotes the interdigitation of pavement cells, whereas reduction of the endogenous auxin synthesis hinders the process. The plants with reduced expression of two functionally redundant ROP/Rac GTPases, ROP2 and ROP4, experienced a similar phenotypic change in lobe formation, as did a quadruple mutant of *YUCCA*-family genes, in which *in vivo* auxin synthesis is severely compromised (Fu et al., 2002, 2005). However, unlike in the *yuc* quadruple mutant, external auxin treatment did not rescue the interdigitation defect of the *ROP2RNAi rop4-1* mutant (Xu et al., 2010). All these observations suggest that ROP2 and ROP4 are involved in sensing/signaling of auxin. Then, Xu and colleagues

(2010) showed that PM-located ROP2 was rapidly (within 30 s) activated after external auxin application. Importantly, this rapid response was abolished in the *abp1-5* mutant, which contains a point mutation in the auxin-binding pocket and exhibits a pavement cell phenotype like the *yuc* quadruple mutant except that the interdigitation defect in *abp1-5* was not rescued by exogenous auxin. These results suggest that ABP1 is involved in the perception of auxin that activates ROP2 signaling in pavement cell morphogenesis.

Auxin has been reported to inhibit PIN internalization (Paciorek et al., 2005; Dhonukshe et al., 2008). Consistently, Xu and colleagues (2010) showed that PIN1 internalization is greatly increased in the *ROP2RNAi rop4-1* plants, as well as in the plants with disruption of ABP1 function. PIN1 is localized to the lobe tip PM where ROP2 is activated (Fu et al., 2005) and is required for lobe formation, as is ROP2. These results suggest that the PIN1-directed auxin efflux is involved in the positive feedback regulation of ROP2 (Fu et al., 2002, 2005). Furthermore, auxin also locally activates the ROP6–RIC1 pathway in an ABP1-dependent manner, which promotes the organization of cortical microtubules and corresponding indentation formation (Fu et al., 2005, 2009; Xu et al., 2010). Taken together, though lacking the direct evidence of where the functional ABP1 in this pathway is located, these results imply that this ABP1-mediated auxin reception occurs at the PM of pavement cells, and then rapidly activates the ROP2–ROP4 pathway to direct PIN1 localization to the lobe tip as well as the ROP6 pathway to coordinate indentation in the complementary side of the neighboring cell (Figure 1).

Importantly, these findings clearly demonstrate that ROP GTPase signaling acts downstream of ABP1 to regulate nontranscriptional responses such as cytoskeletal reorganization and PIN protein distribution that are important for cell polarization and morphogenesis in pavement cells. For the first time, these findings connect a plant-specific signal (auxin) to the conserved function of Rho-family GTPases (ROPs) in the spatial regulation of fundamental processes in plants. It is also noteworthy that this ABP1/ROP-based mechanism for cell morphogenesis and polarity formation may apply to other plant tissues as well. The auxin-coordinated PIN polarization has been implicated in different tissues to establish oriented auxin flow (Petrasek et al., 2006; Mravec et al., 2008; Zhang et al., 2010b), and the *Arabidopsis* ICR1 ROP-interacting protein affects PIN localization in embryos and regulates PIN recycling in roots (Lavy et al., 2007; Hazak et al., 2010). The conservation of the ABP1–ROP signaling pathway in the regulation of PIN localization is further supported by a recent report of ABP1 regulation of PIN endocytosis (see below) as well as the finding that phosphorylation-mediated PIN polarity switch, which was initially demonstrated in bipolar root and shoot cells (Friml et al., 2004; Michniewicz et al., 2007; Li et al., 2011), is also conserved in the multi-polar pavement cells (Li et al., 2011). Determining the function of ROP signaling in the regulation of PIN polarization may help to fill the major gap in auxin biology, such as the identities of the developmental signals and how they control PIN polarization.

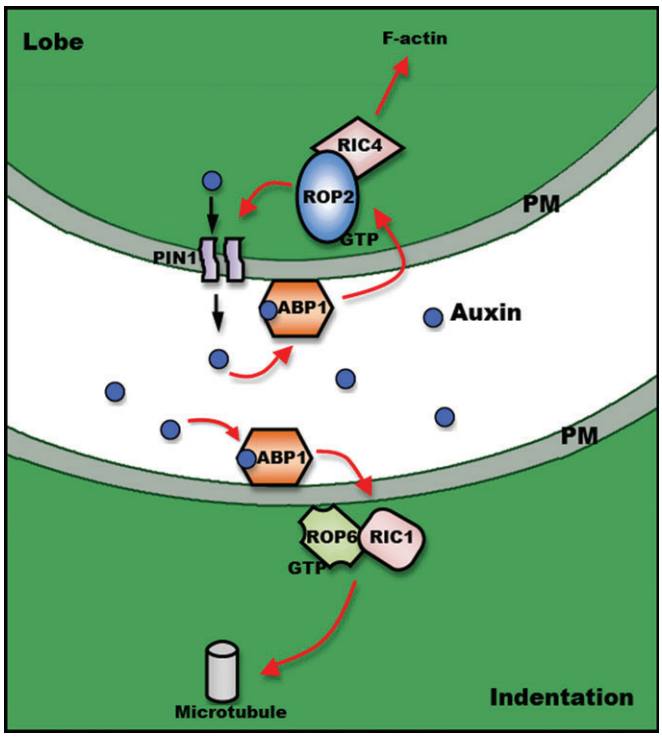


**Figure 1.** Auxin Coordination of Interdigitated Growth in Pavement Cells via the New ABP1–ROP Auxin Signaling Pathways. Two antagonizing ROP GTPase signaling pathways are activated simultaneously by auxin-mediated ABP1 regulation. The PIN1-directed auxin efflux is proposed to be a self-regulated process through the positive feedback loop auxin–ROP2–PIN1–auxin.

## ABP1-MEDIATED ENDOCYTOSIS IS INHIBITED BY AUXIN

The identification of IAA analogs that specifically affect either gene expression or PIN internalization suggests that auxin perception upstream of these regulations involves distinct auxin binding sites, implying that auxin utilizes different signaling pathways for mediating these effects (Robert et al., 2010). Using lines with reduced TIR1/AFB function, Robert and colleagues showed that PIN internalization was not inhibited, suggesting that auxin effect on PIN internalization does not require the TIR1-mediated nuclear signaling pathway. The authors also demonstrated that ABP1 functions as a positive regulator of clathrin-dependent endocytosis including PIN internalization. In *Arabidopsis* root cells, treatments with the vesicle trafficking inhibitor brefeldin A (BFA) induced PIN1 accumulation in a BFA body (Geldner et al., 2001), and auxin reverses this effect, suggesting that auxin inhibits PIN1 internalization (Paciorek et al., 2005). In *Arabidopsis* roots, the *abp1-5* mutation renders root cells insensitive to auxin inhibition of PIN1 accumulation in BFA bodies (Robert et al., 2010).

Furthermore, the down-regulation of ABP1 induced a reduction in PIN1-containing BFA bodies, whereas overexpression of ABP1ΔKDEL, in which the ER retention signal is removed, increased these BFA bodies. Given the effect of ABP1ΔKDEL, it was suggested that it is the PM-localized, but not ER-localized, ABP1 that regulates PIN1 endocytosis (Robert et al., 2010).

Intracellular accumulation of PIN proteins requires clathrin-dependent endocytosis (Dhonukshe et al., 2007). Auxin inhibits this process by interrupting clathrin recruitment to the PM. Conversely, ABP1 was reported to be a positive regulator of this process by ensuring the correct localization of clathrin at the PM (Robert et al., 2010). In *ABP1* antisense lines, the amount of clathrin that is apparently associated with the PM was reduced (Robert et al., 2010). The *abp1-5* mutation was found to inhibit auxin-induced depletion of this apparent PM association of clathrin. Based on these observations, Robert and colleagues (2010) propose that ABP1 promotes the clathrin-dependent endocytosis of PIN1 protein and that auxin binding to ABP1 inhibits ABP1's activity to promote PIN internalization. It should be noted that this model of ABP1's function in the regulation of PIN1 internalization in *Arabidopsis* root epidermal cells contrasts the action of ABP1 in the regulation of PIN1 localization in pavement cells, in which auxin activation of ABP1 was proposed to inhibit PIN1 internalization through ROP2 activation (Xu et al., 2010). These contrasting proposed modes of ABP1 action could be due to differences in different cell types or the complexity of auxin and ABP1 regulation of PIN endocytosis that is not fully understood. Further complication came from Tromas and colleagues' (2010) report showing that PIN localization was not altered in the roots of the same *Arabidopsis* antisense line as used by Robert and colleagues (2010). Clearly, further studies are needed to understand the roles of ABP1 in the regulation of PIN1 trafficking and distribution.

## IS ABP1 FINALLY AN AUXIN RECEPTOR?

Recent studies demonstrate a role for ABP1 in auxin signaling, particularly in the regulation of non-transcriptional auxin responses. The question now is whether there is sufficient evidence to conclude that ABP1 is an auxin receptor. Critics of the notion of "auxin receptor" would argue that none of these studies unambiguously proves that ABP1 functions as an auxin receptor. Undoubtedly, however, these studies have revitalized the 30-year-old hypothesis that ABP1 is an auxin receptor. Prior to these studies, the strongest argument against ABP1's receptor role was that no downstream signaling events were clearly known for ABP1 (Dharmasiri and Estelle, 2004). Xu et al. (2010) now show that ROP signaling is downstream of ABP1. The fact that ABP1-dependent ROP activation by auxin occurs in seconds suggests that ABP1 participation in auxin-mediated ROP activation is direct and occurs at the PM. Another argument against ABP1's role as an auxin receptor is that auxin binding does not change ABP1 conformation based on crystal structural analysis. Given the evidence that cell surface-localized ABP1 is involved in auxin signaling (Napier et al., 2002; Robert et al., 2010) and that auxin activation of ROPs *in vivo* requires PIN1 (Xu et al., 2010), we propose that ABP1 acts as a cell surface auxin receptor to activate cytoplasmic signaling. Secreted ABP1 must interact with a transmembrane protein for the transmission of the auxin signal to ROPs that are localized to the inner face of the PM.

Crystal structure analysis of ABP1 protein shows that the auxin-binding site is situated near the C-terminus region, which sticks out from the central hydrophobic pocket (Woo et al., 2002). This stick structure was predicted to facilitate the interaction between ABP1 and a 'docking protein' on the PM. One docking protein is likely to be CBP1 discussed above. Considering auxin-binding pocket in ABP1 is relatively wide open (Xu et al., 2010), we speculate that the C-terminal region of ABP1 might also interact with an auxin co-receptor that could be involved in the transmembrane transmission of the extracellular auxin signal (Figure 2). Such a co-receptor may interact with ABP1 and auxin in a manner similar to the TIR1–auxin–AUX/IAA complex, in which auxin acts as a glue to stabilize TIR1–AUX/IAA complex without altering the conformation of the TIR1 auxin receptor (Tan et al., 2007). If so, this could explain why auxin binding to ABP1 does not affect its structure. Nonetheless, a major piece missing in this hypothesis, which is important for the final proof of ABP1's role as auxin receptor, is how auxin signal is transmitted from ABP1 to ROPs.

A role for ABP1 as a cell surface receptor does not exclude an additional role for ABP1 in auxin signaling in the ER, where the majority of ABP1 resides. ROP activation requires guanine nucleotide-exchange factors (GEFs) (Yang, 2008). As a member of RhoGEFs, the gene SPIKE1 (SPK1) is known to function in the regulation of cell shape formation (Qiu et al., 2002). A recent

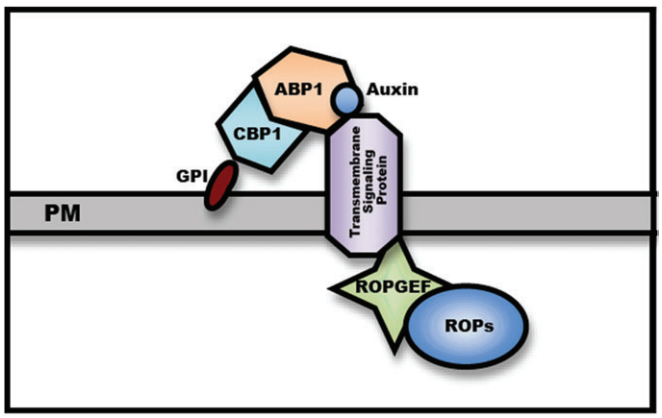


**Figure 2.** A Hypothetic Model for the ABP1-Based Cell–Surface Auxin Receptor Complex. An GPI-anchored protein (CBP1) is proposed to bind the C-terminus masking the C-terminal KDEL ER-retention signal and facilitating ABP1 secretion to the PM. CBP1 alone is unlikely to transmit auxin signal across the PM. A transmembrane protein is speculated to act as an auxin co-receptor with ABP1 to transmit the auxin signal to PM-localized RopGEFs that activate ROPs at the PM.

study suggests that SPK1 is associated with ER exit sites (ERES) (Zhang et al., 2010a). The linking mechanism between ERES-located SPK1 and ROP signaling is still unknown. It would be interesting to elucidate to what extent this linking mechanism correlates with ER-located ABP1.

## CONCLUSIONS AND FUTURE CHALLENGES

With the discovery of the downstream ROP signaling pathways and the important regulatory role in clathrin-mediated endocytosis, ABP1 is back on the stage as a strong candidate for an auxin receptor after a 30-year debate. To confirm its role as an auxin receptor, it is crucial to understand how ABP1 senses auxin at the cell surface and then transmits the signal into the cell. More evidence is needed for the existence of the so-called 'docking protein' and how it collaborates with ABP1 to accomplish the auxin signal transduction. The fact that most reported ABP1 functions at the PM does not exclude the possibility of its functions in ER. To determine whether ABP1 is involved in ER-based auxin signaling will be one of the challenges for the future. Another exciting challenge will be to elucidate how the ABP1- and TIR1/AFBs-based auxin perception/signaling mechanisms coordinate with each other to regulate the diverse auxin-dependent processes. In short, recent progress on ABP1 opens up many new research opportunities in auxin biology.

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